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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/761,435

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Pablo Umana

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3728

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7590

05/26/2009

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EXAMINER

BURKHART, MICHAEL D

ART UNIT

PAPER NUMBER

1633

MAIL DATE

DELIVERY MODE

05/26/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/761,435	Applicant(s) UMANA ET AL.	
	Examiner Michael Burkhart	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12/8/2008; 2/5/2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1-286 is/are pending in the application.
- 4a) Of the above claim(s) See Continuation Sheet is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 30-34, 65-68, 73, 74, 82-95, 186, 188-190, 195, and 206-212 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>1/4/08; 5/23/08; 4/8/09</u> . | 6) <input type="checkbox"/> Other: _____ |

Continuation of Disposition of Claims: Claims withdrawn from consideration are 1-29,35-64,69-72,75-81,96-185,187,191-194,196-205 and 213-286.

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DETAILED ACTION

Receipt and entry of the amendment dated 12/28/2008 is acknowledged. After entry of the amendment, claims 1-286 are pending. Claims 1-29, 35-64, 69-72, 75-81, 96-185, 187, 191-194, 196-205 and 213-286 remain withdrawn as directed to non-elected inventions.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Election/Restrictions

This application contains claims 1-29, 35-64, 69-72, 75-81, 96-185, 187, 191-194, 196-205 and 213-286 drawn to inventions nonelected with traverse in the replies filed on 2/14/2007 and 7/16/2007. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Information Disclosure Statement

The NPL77 reference on the IDS dated 5/23/2008 is a duplicate of NPL81, considered in the IDS dated 4/8/2009, and thus has been lined through. Likewise, the FP3 reference on the IDS dated 1/4/2008 is a duplicate of WO 01/29242 A2, made of record in the Office Action dated 10/3/2007.

Claim Objections

Claim 186 is objected to because of the following informalities: "at least one a" in line 4 should be "at least one". Appropriate correction is required.

Claim Rejections - 35 USC § 102

Claims 30-34, 65-67, 73, 74, 82-95, 186, 188, 189, 195 and 206-212 are rejected under 35 U.S.C. 102(b) as being anticipated by Umana et al (WO 99/54342, cited by applicants, IDS of 5/23/2008) as evidenced by Grabenhorst et al (1999, JBC) and Shields et al (JBC, 2002, of record). **This is a new rejection necessitated by amendment of the claims to recite mammalian cells, a limitation not previously found in the claims.**

Umana et al teach mammalian cell lines (i.e. CHO hamster cells) modified to express the GnT III enzyme as a fusion protein with various tags, such as GFP or myc-tags, along with various IgG molecules. See pages 27-28, 34-38, and 44. Umana et al teach the GnTIII is a Golgi enzyme (e.g. page 39); Grabenhorst et al reinforce this, and teach that it inherently has a Golgi localization domain (see Fig. 2, Table I and page 36110, second column, first full ¶ of Grabenhorst et al in particular). The antibodies of Umana et al may be IgG1 which inherently have an Fc region, absent evidence to the contrary (page 31, last ¶). The antibody molecules expressed may be fusion proteins having an Fc region (page 24). Regarding claim 67, the rat GntIII (page 26) used by Umana et al is considered to comprise a heterologous Golgi localization domain relative to the hamster CHO cell lines. The antibodies produced in the CHO-GnTIII cell lines had increased Fc-mediated cellular toxicity, or ADCC (page 38), linked to the increased

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expression of GnTIII. Umana et al teach that ADCC is mediated by FcγRs (page 21), and that there was an increase in bisected, complex oligosaccharides in the Fc region (page 9). Umana et al teach that expression of GnTIII reduces the amount of bisected, hybrid fucosylated oligosaccharides (page 38) because oligosaccharides modified by GnTIII are no longer substrates for fucosylation. Thus, in relation to antibodies produced in unmodified CHO cells, which do not express significant levels of GnTIII (page 9), the methods of Umana et al using GnTIII expression in CHO cells is considered to have resulted in an increased proportion of nonfucosylated oligosaccharides relative to antibodies produced in unmodified CHO cells. Shields et al teach this lack of fucosylation inherently leads to an increase in FcγRIIIA affinity. Furthermore, at least one type of non-fucosylated bisected, complex oligosaccharide (m/z 1705, Figs 10 and 11) was found in an increased proportion in CHO cells expressing GnTIII (Fig. 9C, D, or E) relative to Sp2/0 cells (Fig. 9A). Regarding claims 92-95 and 209-212, the results of Umana et al indicate that up to 45-50% of the glycans are bisected, non-fucosylated upon expression of GnT-III (page 37, and Figures 9-10).

Regarding claim 83, the instant specification (§ [0031] of the published application) teaches FcγRIIIA to be an activating receptor.

Regarding claim 186, Umana et al teach that the cells of their invention may also comprise mannosidase II, or Man II, which may be expressed with GnTIII (pages 7 and 13). Absent evidence to the contrary, the GnTIII used by Umana et al has a catalytic domain because it performed the catalytic function of the enzyme for reason set forth above, i.e. it added the bisecting GlcNAc to oligosaccharides.

Claim Rejections - 35 USC § 103

Claims 68 and 190 are rejected under 35 U.S.C. 103(a) as being unpatentable over Umana et al (WO 99/54342,) as evidenced by Grabenhorst et al (1999, JBC) and Shields et al (JBC, 2002, of record) in view of Russell et al (WO 01/29242 A2, 2001) and Rabouille et al (1995, J. Cell Sci., cited by applicants). **This is a new rejection necessitated by amendment of the claims.**

The teachings of Umana, Grabenhorst and Shields et al are as above and applied as before. In addition, Umana et al suggest that in order to improve the glycosylation pattern of antibodies for increased ADCC, it would be desirable to re-distribute the GalT enzyme by exchanging its transmembrane domain (i.e. its localization domain) with that of another enzyme found in the trans Golgi network, e.g. α 2,6-sialyltransferase, such that GalT would be further removed from competition with GnTIII for substrates (see also Figs 10 and 11, illustrating the pathway at issue, and how GalT and GnTIII compete for, at least, the M_3Gn_2 substrate). See pages 38-39. Furthermore, Grabenhorst et al teach the routine modification of Golgi-resident enzymes by replacement of the localization domain, or CTS, with those of another. See the abstract, Fig. 2, and Table I in particular. Grabenhorst also teach that mannosidase II and GnTI (*medial* Golgi) are located before GalT in the Golgi network (abstract, top of column 2, page 36107), and that GnTIII is located after GnTI, but before GalT.

None of Umana, Grabenhorst or Shields et al teach the use of the Man II CTS to modify the GnTIII enzyme.

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Russell et al teach modifying the glycosylation of heterologous proteins, such as antibodies, by expression of fusion proteins comprising a post-translational modification enzyme and the "CMS" region of glycosyltransferases or hydrolases located at a desired point in the glycosylation pathway. The CMS region is taught to be the region that determines spatial distribution of a protein in the ER and/or Golgi, and is considered an synonym for the term "CTS" used by Grabenhorst et al. See Example 3, beginning on page 69. Russell et al disclose that post-translational modification enzymes include the general use of N-acetylglucosaminyltransferases (page 8, last ¶) and β -1,4 N-acetylglucosaminyltransferase III (GnT-III) specifically (page 52, first ¶). CMS regions to be used are from enzymes that prepare the glycans for subsequent fucosyl and xylosyl addition, such as mannosidase II (Mann II). See page 69, line 24 to page 70, first full ¶, and Figure 16.

Rabouille teach that Mann II is a *medial* Golgi enzyme that occurs in the ER/Golgi pathway prior to the *trans* Golgi and *trans*-Golgi network enzyme GalT. See the abstract and Introduction on page 1617.

The claimed method of modifying a glycosylation profile is essentially disclosed by Umana et al with the exception of using a Mann II CTS domain in fusion with the GnTIII enzyme in order to relocate the GnTIII in the Golgi pathway. The ordinary skilled artisan, seeking a method to modify the glycosylation profile of antibodies for increased ADCC, would have been motivated to use a Mann II CTS in a fusion polypeptide with GnTIII because Umana et al teaches the desirability of locating GnTIII before GalT in the Golgi pathway, and suggests relocation of one of these enzymes (GalT) after GnTIII in the pathway by replacing the native GalT CTS with that of a later enzyme in the pathway. The teachings of Russell et al regarding

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the use of a heterologous CTS to modify the location of glycosylation enzymes in the Golgi pathway, coupled with the teachings of Rabouille and Grabenhorst et al regarding the location of Mann II prior to GalT in the Golgi pathway present an obvious alternative solution to relocating GnTIII prior to GalT in this pathway. It would have been obvious for the skilled artisan to do this because of the known benefit of generating increased ADCC by glycosylation modification as taught by Umana et al. Given the teachings of the cited references and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered, absent evidence to the contrary, that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Burkhardt whose telephone number is (571)272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Burkhardt/
Primary Examiner, Art Unit 1633